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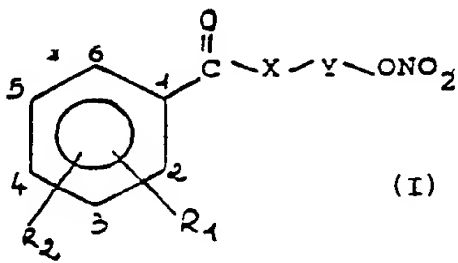
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<b>(21) International Application Number:</b> PCT/EP91/01326 <b>(22) International Filing Date:</b> 15 July 1991 (15.07.91)  <b>(30) Priority data:</b> 21075 A/90 26 July 1990 (26.07.90) IT  <b>(71) Applicant (for all designated States except US):</b> ITALFARM-ACO S.P.A. [IT/IT]; Viale Fulvio Testi, 330, I-20126 Milano (IT).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> SALA, Alberto [IT/IT]; BANFI, Aldo [IT/IT]; BENEDINI, Francesca [IT/IT]; CEREDA, Roberta [IT/IT]; Viale Fulvio Testi, 330, I-20126 Milano (IT).  <b>(74) Agent:</b> MINOJA, Fabrizio; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).		<b>(81) Designated States:</b> AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL (European patent), NO, PL, RO, SD, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> BENZOIC ACID SUBSTITUTED DERIVATIVES HAVING CARDIOVASCULAR ACTIVITY  <div style="text-align: center;"><p>(I)</p></div>  <b>(57) Abstract</b>  Compounds of formula (I) wherein X, Y, R <sub>1</sub> and R <sub>2</sub> have the meanings specified in the specification, are endowed with cardiovascular activity.		

# + DESIGNATIONS OF "SU"

It is not yet known for which States of the former Soviet Union any designation of the Soviet Union has effect.

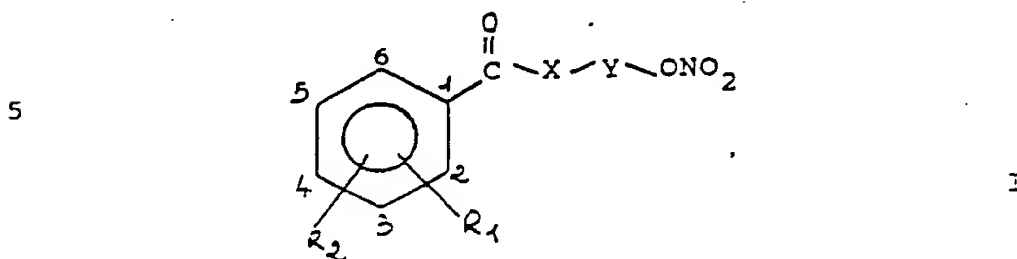
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BENZOIC ACID SUBSTITUTED DERIVATIVES HAVING CARDIOVA-  
SCULAR ACTIVITY

The present invention relates to novel benzoic acid substituted derivatives of general formula (I)



wherein:

- 10 X is an oxygen atom or the NH group;  
Y is ethylene or a C<sub>3</sub>-C<sub>6</sub> straight or branched alkylene, or a cyclopentylene, cyclohexylene or cycloheptylene group;
- 15 R<sub>1</sub> is the OCOR<sub>3</sub> group, wherein R<sub>3</sub> is methyl, ethyl or C<sub>3</sub>-C<sub>5</sub> straight or branched alkyl, or the residue from a 5- or 6- membered monocyclic heterocycle which can be aromatic or partially or totally hydrogenated, containing one or more hetero-atoms selected independently from O, N and S;
- 20 R<sub>2</sub> is hydrogen, hydroxy, halogen, (C<sub>1-4</sub>) alkyl, (C<sub>1-4</sub>)alkoxyl, trifluoromethyl, sulfo, nitro, amino, or mono- or di-(C<sub>1-4</sub>) alkylamino;
- R<sub>1</sub> and R<sub>2</sub>, taken together, are the methylenedioxy group; with the proviso that, when X is NH, Y is ethylene and R<sub>2</sub> is hydrogen, R<sub>1</sub> cannot be the OCOR<sub>3</sub> group at the 2- position in which R<sub>3</sub> is methyl;
- 25 and the pharmaceutically acceptable acid salts thereof.

Compounds having a substituted amido group with a

O<sub>2</sub>NO-alkylene chain are known in literature, including patent literature. For example, substances in which this group is bound to a heterocyclic aromatic ring are described in EP-A 300,400 and in US-P 4,200,640. On the other hand, compounds in which said group is bound to a benzene ring are described in EP-A-83,256 and in Japanese published Patent application 54-81222.

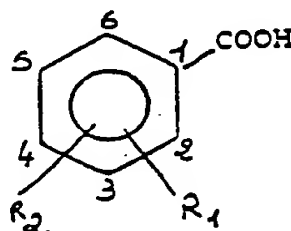
In the compounds of formula I, Y is preferably ethylene or C<sub>3-6</sub> straight alkylene; R<sub>3</sub> is methyl, ethyl or a C<sub>3</sub>-C<sub>6</sub> alkyl group or a heterocyclic group selected from 2-piperidinyl, 4-piperidinyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-thiazolidinyl, 2-furyl; R<sub>2</sub> is hydrogen, halogen, nitro, methoxy or sulpho.

Preferred compounds of formula I are those wherein X is oxygen or NH, R<sub>1</sub> is acetoxy (R<sub>3</sub> = methyl) or 4-thiazolidinylcarbonyloxy, Y and R<sub>2</sub> having the above defined meanings.

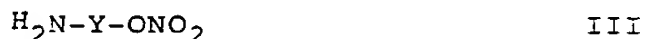
Particularly preferred compounds of formula I are those wherein X is oxygen or NH, R<sub>1</sub> is acetoxy, Y is ethylene, R<sub>2</sub> is hydrogen or halogen. R<sub>1</sub> is preferably in the 4- or 3-position.

Compounds of formula (I) can be obtained using the techniques described hereinbelow.

Thus, for instance, when compounds in which X is the NH group are desired, a molar amount of a benzoic acid of formula



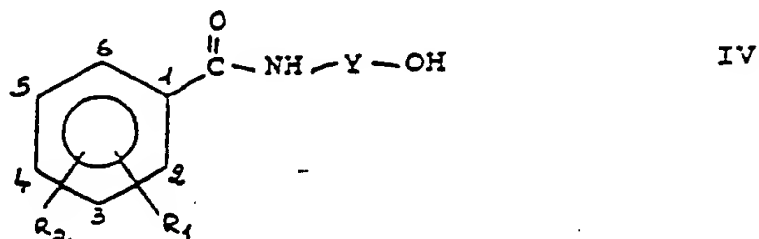
wherein  $R_1$  and  $R_2$  are as defined above, or of a functional reactive derivative thereof, such as an halide or an anhydride of either the same acid of formula (II) or mixed, is reacted with a substantially equimolecular amount of an amino-alkanol nitric ester, of formula



wherein Y is as defined above, or of a salt thereof, such as a halide or a nitrate.

The reaction is carried out in water or in an organic solvent, such as a halogenated aliphatic hydrocarbon, or in water/organic solvent mixtures, at a temperature ranging from 0°C to room temperature and is complete within a time from about 1 hour to about 3 hours. When the compound of formula (III) is used in form of a salt thereof, the reaction is preferably carried out also in the presence of an organic or inorganic base. Generally a molar excess of an alkali or alkaline-earth metal carbonate or bicarbonate, or of a nitrogen organic base, such as trimethylamine, triethylamine, pyridine and the like, is used, said excess being calculated over the compound of formula (II).

Sometimes it can be more convenient to introduce the  $NO_2$  group on the already formed amide of formula

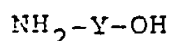


wherein  $R_1$ ,  $R_2$  and Y have the above mentioned meanings.

This procedure can advantageously be used instead of the above described one, when amides within formula (I), in which Y is a C<sub>3-6</sub> straight or branched alkylene or a cyclopentylene, cyclohexylene or cycloheptylene group, are desired.

In fact, corresponding nitric esters of the amino-alkanols to be condensed with the compound of formula (II) or with a functional derivative thereof, are slightly instable under the used reaction conditions, so that the final products are obtained in low yields or contaminated by undesired impurities.

According to this method, the starting benzoic acid of formula (II) is converted into a functional derivative thereof, for instance by reacting it with an alkyl-haloformate, to obtain a mixed anhydride. A molar amount of this anhydride is then treated with a substantially equivalent molar amount of an aminoalkanol of formula



V

wherein Y is as defined above, in an inert organic solvent, such as a (C<sub>1-4</sub>) halogenated aliphatic hydrocarbon, at a temperature ranging from -5°C to about 10°C. An amide of formula (IV) is obtained which can be either recovered and characterized, or used as such for the following steps. Thus, for instance, a molar amount of this substance can be reacted with a molar excess of trifluoromethanesulfonic anhydride and of a tetraalkylammonium nitrate, at a starting temperature from -60 to about -40°C. Even though the amounts of trifluoromethanesulfonic anhydride and tetraalkylammonium nitrate are not critical to the progress of the

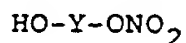


reaction, it is preferred to use about 2 or more molar equivalents of these reagents per mole of starting anhydride. It has also been noted that, when Y is cyclopentylene, cyclohexylene or cycloheptylene, substituting the hydroxy group with the  $\text{ONO}_2$  group can involve an inversion in steric configuration.

The reaction can be carried out in a number of polar or apolar organic solvents. For example,  $\text{C}_{1-4}$  halogenated aliphatic hydrocarbons, benzene, toluene, cyclohexane, dioxane, tetrahydrofuran, lower alkyl esters of lower aliphatic acids, di- $(\text{C}_{1-4})$ alkyl esters, pyridine, dimethylsulfoxide, dimethylformamide, dimethylacetamide, acetonitrile and mixtures thereof, can advantageously be used.

After about two hours, the reaction temperature is raised to about 25-50°C and kept for a time ranging from about 1 to about 4 hours, thereafter the reaction mixture is worked up according to the usual techniques.

The procedures described hereinbefore can advantageously be used also for the preparation of compounds of formula (I) in which Y,  $\text{R}_1$  and  $\text{R}_2$  are as defined above and X is an oxygen atom, by reacting, for example, a compound of formula (II), or a functional derivative thereof, with either the suitable mononitric ester of an  $\alpha$ - $\omega$ -bis-alkanol of formula



VI

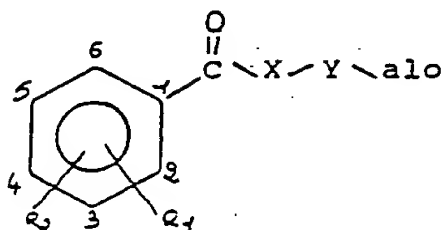
or 1', $\omega$ -bis-alkanol itself, in which case the  $\text{ONO}_2$  group is then introduced by means of the already described techniques.

Alternatively, the starting compound of formula (II), or a functional derivative thereof, can be

reacted with a haloalkylamine or a haloalcohol of formula



wherein X and Y have the above mentioned meanings and halo is a halogen atom, to obtain compounds of formula



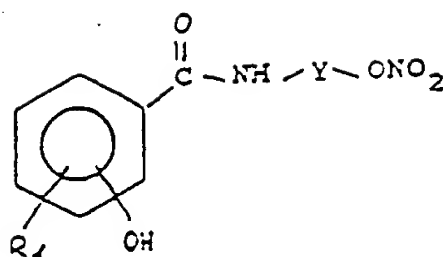
VIII

wherein  $R_1$  and  $R_2$  have the above mentioned meanings, which compounds are then reacted with  $\text{AgNO}_3$ .

These reactions are effected in an inert organic solvent, such as a halogenated aliphatic hydrocarbon, at room temperature, using a slight molar excess of compound (VII) with respect to the starting benzoic acid (II), or a functional derivative thereof. Silver nitrate is used in equimolecular amounts about twofold those of compound (VIII) which can be either recovered and characterized, or used directly for the subsequent step.

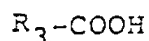
Compounds of formula (I) wherein X is NH, Y and  $R_2$  are as defined above and  $R_1$  is a  $\text{OCOR}_3$  group, in which  $R_3$  is as defined above, and it can be at the 2-position when  $R_2$  is hydrogen, Y is ethylene and  $R_3$  is methyl, are in their turn suitable starting material for the preparation of other compounds according to the invention, falling within general formula (I).

Thus, if the  $\text{OCOR}_3$  group is subjected to hydrolysis, to obtain compounds of formula



IX

wherein Y and  $R_2$  have the above mentioned meanings, and the free hydroxyl of the resulting compound is acylated with an acid of formula



X

wherein  $R_3$  is as defined above, or with a functional derivative of said acid, such as a halide or a symmetrical or mixed anhydride, other substances of formula (I) can be prepared, in which the  $R_3$  group, deriving from the acid of formula (X) or from a functional derivative thereof, is different from that of the starting product.

The compounds of formula (IX), as well as the pharmaceutically acceptable salts thereof, have cardiovascular activity and therefore are a further object of the present invention.

The procedure described above is used advantageously but not only, when compounds of formula (I) wherein  $R_3$  is a residue from a heterocycle, are desired.

Whenever a  $\begin{array}{c} \diagup \text{N} \diagdown \\ | \\ \text{H} \end{array}$  is present in the heterocyclic

residue, compound (X) is preferably used in form of a functional derivative thereof, such as a mixed anhydride, said group optionally being protected previously by means of conventional protecting agents,

such as bis-tert-butyl-dicarbonate, tert-butyl-dimethyl-silyl-chloride and the like.

Other obvious reactions allowing to transform compounds of formula (I) into other compounds of the same general formula are to be considered falling  
5 within the scope of the invention.

As stated above, the compounds of the invention have cardiovascular activity. Particularly, they showed marked in vitro vasorelaxing activity and a remarkable  
10 antianginal activity in the test animal. Such favourable biological properties are associated to a negligible hypotensive effect, whereas it is well known that one of the most severe side-effects of the nitro-derivatives already known and used in therapy is  
15 the onset of a marked postural hypotension, which in some cases can cause loss of consciousness, particularly if the patient remains in an erect position (Goodman and Gilman, The Pharmacological Bases of Therapeutics, 7<sup>th</sup> edition, page 813). Therefore, the  
20 compounds of the invention can be considered potential drugs having a specifically antianginal activity. They proved to have also an antiarrhythmic activity, which is another valuable feature, since angina attacks are often associated to more or less marked arrhythmias.

25 The in vitro vasorelaxing activity of the compounds of the present invention was evaluated in the test of the noradrenaline-contracted rat aorta strip. The test was carried out according to the procedure described by K. Murakami et al., Eur. J. Pharmacol.,  
30 141, 195, 1987. The IC<sub>50</sub> values, i.e. the concentration of active substance, expressed in mol/l,

inhibiting by 50% the aorta strip contraction, were evaluated.

The results obtained for some representative compounds of the invention are reported in the following Table 1.

TABLE 1

Compound of Example	<u>in vitro</u> vasorelaxing activity IC <sub>50</sub> (mol/l)
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10

1	$1,6 \times 10^{-7}$
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2	$2,3 \times 10^{-6}$
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3 B	$1,2 \times 10^{-6}$
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4 B	$1,1 \times 10^{-7}$
-----	----------------------

15

8 B	$1,3 \times 10^{-8}$
-----	----------------------

9 A	$1,6 \times 10^{-7}$
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9	$5,4 \times 10^{-7}$
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In vivo antianginal activity was evaluated in Sprague Dawley anesthetized rats of 350-400 g mean weight, according to the procedure by M. Leitold et al., *Arzneim. Forsch.* 36, 1454, 1986. The test was carried out by intravenously administering to the animal one I.U./kg (equivalent to 3 mg/kg) of Arg-vasopressine inducing a choronatic spasm which can be reproduced and electrocardiographically evidenced by an increase in the T wave. The compounds of the invention were administered through a gastric probe at a dose of 3 mg/kg, one hour before administering Arg-vasopressine. The antianginal effect was expressed as percent inhibition of the increase in T wave versus controls.

The results obtained for some representative compounds of the invention are reported in Table 2.

TABLE 2

Compound of Example	% Inhibition of the increase in T waves versus controls
2	55
4 B	53
8 B	61
9 A	42

The hypotensive effect was evaluated in the anesthetized rat. Male Sprague Dawle rats, weighing 350-400 g, anesthetized with urethane (1.25 g/kg i.p.) were used. Arterial pressure was monitored by means of a catheter inserted in left carotide, in its turn connected with a pressure transducer. The compounds of the invention were administered in bolus, in the femoral vein, at increasing doses and the hypotensive effect was evaluated as the percent reduction in mean arterial pressure compared with basal values. Thereafter, the relative potency of the compounds of the invention was measured as  $ED_{20}$ , i.e. the amount reducing pressure by 20%.

Tests effected on representative compounds of the invention proved that the  $ED_{20}$  were higher than 0.5 mg/kg body weight.

Moreover, such favourable biological properties are associated with a low toxicity: in fact the  $LD_{50}$  values, determined according to the method by

Lichtfield and Wilcoxon, J. Pharm. Expt. Ther. 96, 99, 1949, were higher than 500 mg/kg i.p.

The present invention also relates to the use of the novel compounds of the invention as antianginal agents, as well as to all of the acts and aspects which can industrially apply to said use, including the incorporation of said compounds in pharmaceutical compositions. Examples of said pharmaceutical compositions are tablets, dragees, syrups and vials, the latter suitable for both the oral and the intramuscular or intravenous administrations. Said compositions will contain the active ingredient alone or in admixture with the usual pharmaceutically acceptable excipients and carriers.

The doses of the active ingredient for the cure of the anginal attacks can range within wide limits, depending on the nature of the used compound. The preferred dosage forms generally contain from about 1 to about 10 mg of the active ingredient, and they are suitable for administration one or more times daily.

The compounds used as the starting material in the following Examples are commercial products, or they can be prepared according to the literature: in this instance, the related references are reported hereinbelow.

- a) 2-Nitrooxyethylamine nitrate - Bull. Soc. Chem. Fr., 11, 470, 1944.
- b) 3-Acetoxy and 4-acetoxy-benzoic and 3-acetoxy-benzoic acid chlorides - Arzneim. Forsch. 14, (4), 324, 1964.
- c) 2-Acetoxy-4-chloro-benzoic acid - JACS, 89, 4853,

1967.

d) 2-Propionyloxy-benzoic acid - J. Biol. Chem., 255, 2816, 1980.

5 e) 3-(Tert.-butoxycarbonyl)-4-thiazolidinyl-carboxylic acid - JACS, 87, 620, 1965.

<sup>1</sup>H-NMR Spectra were carried out in dimethylsulfoxide (DMSO) with a VARIAN GEMINI 200 spectrometer. <sup>13</sup>H-NMR Spectra were performed using a VARIAN GEMINI 200 spectrometer, taking the  
10 dimethylsulfoxide peak at 39.5 p.p.m. as the reference.

The invention is further illustrated by the following Examples.

#### EXAMPLE 1

##### 3-Acetoxy-N-(2-nitroxyethyl)-benzamide

15 18.6 g (0.110 mole) of 2-nitrooxy-ethylamine nitrate at 0°C were added to a solution of 40.7 g (0.458 mole) of sodium bicarbonate in 140 ml of water and 120 ml of chloroform. After stirring for 10 min, 22.5 g (0.113 mole) of 3-acetoxybenzoic acid chloride  
20 were dropped therein and the resulting mixture was stirred for one hour at 0°C. The reaction mixture was warmed to room temperature, the two phases were separated and the organic phase was washed with water and dried over sodium sulfate. The crude title product  
25 was obtained, which was recrystallized from ethyl ether. M.p. 89-91°C. Yield 26.5 g.

#### EXAMPLE 2

##### 4-Acetoxy-N-(2-nitroxyethyl)-benzamide

30 Starting from 0.113 mole of 4-acetoxybenzoic acid chloride and 0.110 mole of 2-nitrooxy-ethylamine nitrate, and operating substantially as described in



the preceding Example, 22 g of the title compound were obtained. M.p. 95-97°C (ethyl ether).

## EXAMPLE 3

3-Acetoxy-N-(5-nitroxypentyl)-benzamide

5 A - 3-Acetoxy-N-(5-hydroxypentyl)-benzamide - 10.5 ml.

(0.111 mole) of ethyl chloroformate were added at 0°C, under stirring, to a solution of 20 g (0.111 mole) of 3-acetoxybenzoic acid in 500 ml of chloroform and 15.3 ml of triethylamine. After one hour at 0°C, a  
10 solution of 11.4 g (0.111 mole) of 5-amino-1-pentanol was added and the resulting reaction mixture was stirred for 4 hours, then it was washed with water and the separated organic phase was dried over sodium sulfate. 31.8 g of the crude product were obtained,  
15 which was purified on a silica gel column, eluting with 91/9 (v/v) ethyl acetate/n-hexane. 7.5 g of the title product were recovered in form of an oil.

B - 3-Acetoxy-N-(5-nitroxypentyl)-benzamide

10.6 g (0.0377 mole) of trifluoromethanesulfonic  
20 anhydride were dropped into a solution of 5 g (0.0188 mole) of the compound prepared in A) and 11.5 g (0.0377 mole) of tetrabutylammonium nitrate in 500 ml of methylene chloride, 3.08 ml of pyridine and 37.5 ml of N,N-dimethylformamide cooled to -50°C. The reaction  
25 mixture was heated to 40°C and kept at this temperature for 3 hours, then it was washed with water, 0.5% aqueous hydrochloric acid, 5% aqueous sodium bicarbonate, then again with water, finally dried over sodium sulfate. After evaporating the solvent, a crude  
30 product was obtained which was purified on a silica gel column. Yield: 4 g of the title compound, in form of an

oil, having the following characteristics:

i) <u>Elemental analysis:</u>	%C	%H	%N
Calculated	54.19	5.85	9.03
Found	54.01	5.92	8.98

5 ii)  $^1\text{H}$ -NMR (in DMSO): characteristic resonance peaks were evidenced at the following  $\delta$  (p.p.m.): 8.54 (t, 1H); 7.74 (dd, 1H); 7.59 (t, 1H); 7.51 (t, 1H); 7.29 (dd, 1H); 4.52 (t, 2H); 3.26 (q, 2H); 1.77÷1.29 (m, 6H)

10 iii)  $^{13}\text{C}$ -NMR (in DMSO): characteristic resonance peaks were evidenced at the following  $\delta$  (p.p.m.): 169.55; 165.44; 150.69; 156.36; 129.67; 124.81; 124.72; 120.89; 73.87; 38.91; 28.47; 25.70; 22.52; 20.72.

#### EXAMPLE 4

##### 2-Acetoxy-N-(5-nitroxypentyl)-benzamide

##### 15 A - 2-Acetoxy-N-(5-hydroxypentyl)-benzamide

The compound was prepared as described in Example 3A, starting from 10 g (0.0555 mole) of acetylsalicylic acid. 5.7 g of a product were obtained, in form of an oil, which was directly used in the subsequent step.

##### 20 B - 2-Acetoxy-N-(5-nitroxyethyl)-benzamide

The title compound was obtained substantially as described in Example 3B. Yield: 3.2 g of a pure product having the following characteristics:

i) <u>Elemental analysis:</u>	%C	%H	%N
25 Calculated	54.19	5.85	9.03
Found	54.35	5.88	9.04

30 ii)  $^1\text{H}$ -NMR (in DMSO): characteristic resonance peaks were evidenced at the following  $\delta$  (p.p.m.): 8.29 (t, 1H); 7.58÷7.46 (m, 2H); 7.33 (t, 1H); 7.18 (d, 1H); 4.53 (t, 2H); 3.20 (q, 2H); 2.21 (s, 3H); 1.77÷1.29 (m, 6H)

iii)  $^{13}\text{C}$ -NMR (in DMSO): characteristic resonance peaks were evidenced at the following  $\delta$  (p.p.m.): 169.15; 165.56; 148.19; 131.25; 129.89; 129.05; 125.96; 123.40; 73.88; 38.53; 28.44; 25.66; 22.41; 20.66.

5

## EXAMPLE 5

2-Acetoxy-N-(cis-2-nitroxycyclohexyl)-benzamideA - 2-Acetoxy-N-(trans-2-hydroxycyclohexyl)-benzamide

Prepared substantially according to the procedure described in Example 3A, starting from 5 g (0.033 mole) of trans-2-hydroxy-cyclohexylamine hydrochloride and 5.9 g (0.33 mole) of acetylsalicylic acid. 2.6 g of the product were obtained, which was used directly in the subsequent step.

B - 2-Acetoxy-N-(cis-2-nitroxycyclohexyl)-benzamide

Prepared according to the procedure described in Example 3B. 1 g of the title compound was obtained. M.p. 143-145°C (chloroform/acetone = 9/1).

## EXAMPLE 6

2-Acetoxy-4-chloro-N-(2-nitroxyethyl)-benzamide

Into a solution of 10 g (0.0466 mole) of 2-acetoxy-4-benzoic acid and 6.5 ml (0.0466 mole) of triethylamine in 250 ml of chloroform, cooled to 5°C were dropped first 4.4 ml (0.0466 mole) of ethyl chloroformate then, one hour later, a solution of 7.9 g (0.0466 mole) of 2-nitroxy-ethylamine nitrate and 6.5 ml (0.0466 mole) of triethylamine in 50 ml of chloroform. The reaction mixture was kept at 0°C under stirring, then washed with 300 ml of water, then with 300 ml of 5% aqueous sodium bicarbonate, dried over sodium sulfate and concentrated. The resulting residue was chromatographed on a silica gel column, eluting

with methylene chloride/acetone = 92/8 (v/v). 6.5 g of the title product were obtained. M.p. 75-77°C (n-hexane).

## EXAMPLE 7

5 N-2-(Nitroxyethyl)-2-propionyloxy-benzamide

The title compound was prepared according to the procedure described in the preceding Example, starting from 5 g (0.0258 mole) of 2-propionyloxy-benzoic acid and 4.4 g (0.0258 mole) of 2-nitrooxyethylamine  
10 nitrate. The residue resulting from the working up of the reaction mixture was chromatographed on a silica gel column, eluting with methylene chloride/acetone = 95/5 (v/v). 4.5 g of the product were obtained, in form of an oil, having the following characteristics:

15	i) <u>Elemental analysis:</u>	%C	%H	%N
	Calculated	51.06	5.00	9.92
	Found	51.1	4.97	9.89

ii) <sup>1</sup>H-NMR (in DMSO): characteristic resonance peaks were evidenced at the following  $\delta$  (p.p.m.): 8.52 (t, 1H); 7.59; 7.46 (m, 2H); 7.33 (t, 1H); 7.18 (d, 1H);  
20 4.59 (t, 2H); 3.53 (q, 2H); 2.55 (q, 2H); 1.10 (t, 3H)

iii) <sup>13</sup>C-NMR (in DMSO): characteristic resonance peaks were evidenced at the following  $\delta$  (p.p.m.): 172.20; 166.16; 147.70; 131.97; 129.41; 127.81; 124.72; 122.15;  
25 72.33; 36.60; 28.50; 9.30.

## EXAMPLE 8

2-Acetoxy-2-nitroxyethylbenzoateA - 2-Acetoxy-2-bromoethylbenzoate

5.6 ml (0.0755 mole) of 2-bromoethanol were added  
30 to a solution of 10 g (0.0504 mole) of 2-acetoxy-benzoyl chloride and 13.6 ml (0.1 mole) of

triethylamine in 200 ml of methylene chloride. The reaction mixture was kept at room temperature for 2.5 hours; then it was washed with water, the organic phases were separated and the organic phase was dried over sodium sulfate. The product was purified on a silica gel column, eluting with n-hexane/ethyl acetate - 75/25 (v/v) to obtain 3 g of the product, in form of an oil, which was used directly in the subsequent step.

B - 2-Acetoxy-2-nitroxyethylbenzoate

The product obtained in step A (0.0105 mole) was dissolved in 15 ml of acetonitrile and a solution of 4.08 g (0.024 mole) of silver nitrate in 28 ml of acetonitrile was added thereto. The resulting mixture was refluxed for 4 hours, shielded from light, then the formed salts were filtered and the solvent was evaporated off. The resulting residue was taken up into methylene chloride, washed with water, the organic phase was recovered, dried over sodium sulfate and concentrated to give a residue which was purified on a silica gel column, eluting with n-hexane/ethyl acetate - 55/45 (v/v). 2 g of the title compound were obtained, having the following characteristics:

25	i) <u>Elemental analysis:</u>	%C	%H	%N
	Calculated	49.08	4.12	5.20
	Found	49.18	4.16	5.16

ii) <sup>1</sup>H-NMR (in DMSO): characteristic resonance peaks were evidenced at the following  $\delta$  (p.p.m.): 7.96 (dd, 1H); 7.71 (dt, 1H); 7.43 (t, 1H); 7.26 (d, 1H); 4.86 (m, 2H); 4.56 (m, 2H); 2.29 (s, 3H);

iii) <sup>13</sup>C-NMR (in DMSO): characteristic resonance peaks were evidenced at the following  $\delta$  (p.p.m.): 169.47;

164.14; 150.36; 134.84; 131.58; 126.57; 124.34; 122.87;  
71.55; 61.13; 20.58.

## EXAMPLE 9

N-(2-Nitroxyethyl)-2-[(4-thiazolidinyl)carbonyloxy]-  
5 benzamide hydrochloride

A - 2-Hydroxy-N-(2-nitroxyethyl)-benzamide

13 g (0.0485 mole) of 2-acetoxy-N-2-  
(nitrooxyethyl)-benzamide (prepared as described in  
Japanese published patent application N° 54-81222) and  
10 1 g (0.0147 mole) of imidazole were dissolved in 223 ml  
of methanol and 44 ml of water, and the resulting  
solution was stirred at room temperature for 12 hours.  
Solvent was evaporated off and the resulting residue  
was taken up into methylene chloride and washed with  
15 water. The organic phase was separated, dried over  
sodium sulfate and evaporated to dryness under reduced  
pressure. The resulting residue was purified on a  
silica gel column, eluting with toluene/methanol = 97/3  
(v/v). 4.5 g of a product were obtained. M.p. 76-78°C  
20 (n-hexane).

B - 2-[(3-tert.-butoxycarbonyl)-4-thiazolidinyl]carbo-  
nyloxy]-N-(2-nitroxyethyl)-benzamide

To 6.2 g (0.0265 mole) of 3-(tert-butoxycarbonyl)-  
4-thiazolidinecarboxylic acid and 3.67 ml (0.0265 mole)  
25 of triethylamine in 50 ml of chloroform were added, at  
0°C, 2.53 ml (0.0265 mole) of ethyl chloroformate and,  
after one hour, 6 g (0.0265 mole) of the compound  
prepared in step A. After that, the reaction mixture  
was stirred at room temperature for 12 hours, the  
30 organic phase was washed with water, separated, dried  
over sodium sulfate and concentrated under reduced

pressure. The residue was purified on silica gel, eluting with chloroform/methanol - 97/3 (v/v). 3.6 g of the product were obtained, which was used directly in the subsequent step.

5 C - N-(2-Nitroxyethyl)-2-[(4-thiazolidinyl)carbonyloxy]-benzamide

The compound obtained in step B (3.5 g, 0.00802 mole) was dissolved in 20 ml of ethyl acetate and this solution was added with 30 ml of a 2.76 M solution of hydrochloric acid in ethyl acetate. The resulting mixture was left to stand for 1 hour, to obtain a precipitate which was recovered by filtration, washed with ethyl acetate and dried. Yield: 2.3 g. M.p. - 164-166°C (ethyl acetate).

15

EXAMPLE 10

2-Nicotinoyloxy-N-(2-nitroxyethyl)-benzamide

To a solution of 2.7 g (0.02211 mole) of nicotinic acid and 3.1 ml (0.0221 mole) of triethylamine in 20 ml of chloroform, kept at 0°C, 2.1 ml (0.0221 mole) of ethyl chloroformate and, after one hour, 5 g (0.0221 mole) of the compound of Example 9A, were added. The mixture was kept at room temperature for 20 hours, the organic phase was washed with water, separated, dried over sodium sulfate and concentrated under reduced pressure. The obtained residue was purified on a silica gel column, eluting with ethyl acetate/n-hexane = 70/30 (v/v). M.p. 94-96°C.

25

EXAMPLE 11

2-Acetoxy-5-nitropentylbenzoate

30 A - 2-Acetoxy-5-bromopentylbenzoate

2-Ac toxy-5-bromopenthylbenzoate was prepared

according to the procedure described in Example 8A, starting from 4.75 g (0.024 moles) 2-acetoxybenzoyl chloride and 6 g (0.036 moles) 5-bromoethanol. 3.5 g product, which was used directly in the subsequent step, were obtained.

B - 2-Acetoxy-5-nitroxypentylbenzoate

The title compound was prepared according to the procedure of Example 8B. The desired product (3 g), in the form of an oil, were obtained with the following characteristics:

- |                               |       |      |      |
|-------------------------------|-------|------|------|
| i) <u>Elemental analysis:</u> | %C    | %H   | %N   |
| Calculated                    | 54.02 | 5.50 | 4.50 |
| Found                         | 54.01 | 5.47 | 4.46 |
- ii) <sup>1</sup>H-NMR (in DMSO): characteristic resonance peaks were evidenced at the following  $\delta$  (p.p.m.): 7.96 (dd, 1H); 7.70 (dt, 1H); 7.43 (t, 1H); 7.26 (t, 1H); 4.55 (t, 2H); 4.25 (t, 2H); 2.24 (s, 3H); 1.82÷1.65 (m, 4H); 1.55÷1.37 (m, 2H)
- iii) <sup>13</sup>C-NMR (in DMSO): characteristic resonance peaks were evidenced at the following  $\delta$  (p.p.m.): 169.35; 164.33; 150.24; 134.47; 131.42; 126.53; 124.29; 123.52; 73.93; 64.86; 27.89; 25.94; 21.94; 21.01.

Following substantially the same procedure described in the above Examples, starting from the appropriate compounds of formula (II) and formula (IX), the following compounds of formula (I) can be prepared:

2-Acetoxy-3-bromo-N-(2-nitroxyethyl)-benzamide

2-Acetoxy-4-diethylamino-N-(2-nitroxyethyl)-benzamide

N-(2-Nitroxyethyl)-2-pentanoyloxy-benzamide

2-Nicotinoyloxy-2-nitroxyethylbenzoate

3-Nicotinoyloxy-2-nitroxyethylbenzoate



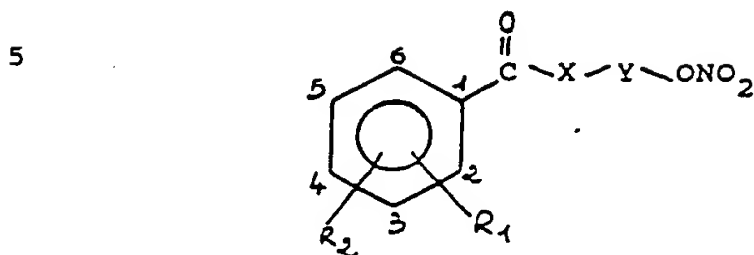
- 3-Nicotinoyloxy-N-(2-nitroxyethyl)-benzamide  
2-Acetoxy-3-nitro-N-(2-nitroxyethyl)-benzamide  
3-Nitro-N-(2-nitroxyethyl)-2-propionyloxy-benzamide  
3-Nitro-N-(2-nitroxypentyl)-2-propionyloxy-benzamide  
5 2-Acetoxy-3-nitro-2-nitroxyethylbenzoate  
2-Nicotinoyloxy-N-(5-nitroxypentyl)-benzamide  
3-Nicotinoyloxy-N-(5-nitroxypentyl)-benzamide  
2-Nicotinoyloxy-5-nitroxypentylbenzoate  
2-Acetoxy-5-chloro-N-(2-nitroxyethyl)-benzamide  
10 2-Acetoxy-N-(2-nitroxyethyl)-4-trifluoromethyl-benzamide  
2-Acetoxy-N-(5-nitroxypentyl)-4-trifluoromethyl-benzamide  
2-Acetoxy-5-fluoro-N-(2-nitroxyethyl)-benzamide  
15 5-Fluoro-3-propionyloxy-2-nitroxyethylbenzoate  
N-(2-Nitroxypropyl)-4-propionyloxy-benzamide  
2-Acetoxy-4-methoxy-N-(2-nitroxyethyl)-benzamide  
2-Acetoxy-4-methoxy-N-(2-nitroxyhexyl)-benzamide  
2-Acetoxy-5-methyl[(2,2-dimethyl-3-nitroxy)propyl]-benzoate  
20 zoate  
2-Acetoxy-5-methoxy-2-nitroxypropylbenzoate  
3-Acetoxy-5-sulpho-2-nitroxyethylbenzoate  
N-(2-Nitroxyethyl)-2-thenoyloxy-benzamide  
N-(2-Nitroxypropyl)-2-(2-furoyloxy)-benzamide  
25 N-(2-Nitroxyethyl)-2-(2-piperidinylcarbonyloxy)-benzamide  
3-Nitro-(2-nitroxypropyl)-2-(2-piperidinylcarbonyloxy)-benzamide  
2-Thenoyloxy-2-nitroxyethylbenzoate  
30 2-Thenoyloxy-2-nitroxybutylbenzoate  
2-(2-Piperidinylcarbonyloxy)-2-nitroxyethylbenzoate

N-(2-Nitroxyethyl)-4-(4-piperidinylcarbonyloxy)-benzamide

3,4-Methylenedioxy-N-(2-nitroxyethyl)-benzamide

CLAIMS

1. Compounds of formula I



10 wherein:

X is an oxygen atom or the NH group;

Y is ethylene or a C<sub>3</sub>-C<sub>6</sub> straight or branched alkylene, or a cyclopentylene, cyclohexylene or cycloheptylene group;

15 R<sub>1</sub> is the OCOR<sub>3</sub> group, wherein R<sub>3</sub> is methyl, ethyl or C<sub>3</sub>-C<sub>5</sub> straight or branched alkyl, or the residue from a 5- or 6- membered monocyclic heterocycle which can be aromatic or partially or totally hydrogenated, containing one or more hetero-atoms selected  
20 independently from O, N and S;

R<sub>2</sub> is hydrogen, hydroxy, halogen, (C<sub>1-4</sub>) alkyl, (C<sub>1-4</sub>)alkoxyl, trifluoromethyl, sulfo, nitro, amino, or mono- or di-(C<sub>1-4</sub>) alkylamino;

R<sub>1</sub> and R<sub>2</sub>, taken together, are the methylenedioxy group; with the proviso that, when X is NH, Y is  
25 ethylene and R<sub>2</sub> is hydrogen, R<sub>1</sub> cannot be the OCOR<sub>3</sub> group at the 2- position in which R<sub>3</sub> is methyl; and the pharmaceutically acceptable acid salts thereof.

2. Compounds according to claim 1 wherein Y is  
30 ethylene or C<sub>3-6</sub> straight alkylene; R<sub>3</sub> is methyl, ethyl or a C<sub>3</sub>-C<sub>6</sub> alkyl group or a heterocyclic group selected

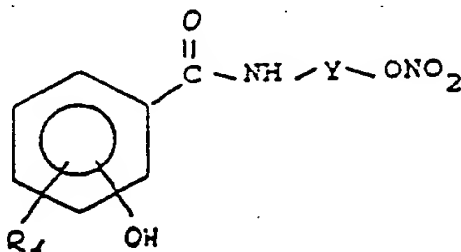
from 2-piperidinyl, 4-piperidinyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-thiazolidinyl, 2-furyl;  $R_2$  is hydrogen, halogen, nitro, methoxy or sulpho.

3. Compounds according to claim 1 wherein X is oxygen or NH,  $R_1$  is acetoxy ( $R_3$  = methyl) or 4-thiazolidinylcarbonyloxy, Y and  $R_2$  are as above defined.

4. Compounds according to claim 1 wherein X is oxygen or NH,  $R_1$  is acetoxy, Y is ethylene,  $R_2$  is hydrogen or halogen.

5. A compound of claims 1-4 selected from  
 4-Acetoxy-N-(2-nitroxyethyl)-benzamide  
 2-Acetoxy-N-(5-nitroxyethyl)-benzamide  
 2-Acetoxy-2-nitroxyethylbenzoate  
 N-(2-Nitroxyethyl)-2-[(4-thiazolidinyl)carbonyloxy]-benzamide hydrochloride

6. Compounds of formula IX



IX

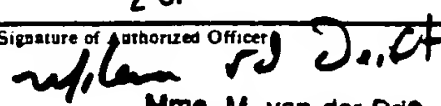
wherein Y and  $R_1$  are as defined for compounds of formula I, for use as medicinal agents.

7. Pharmaceutical compositions containing as the active principle a compound of claims 1-6 in admixture with a pharmaceutically acceptable excipient.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 91/01326

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all:*)		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl.5	C 07 C 235/48	C 07 C 235/60
C 07 C 203/04	C 07 D 213/80	C 07 D 211/60
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched*		
Classification System	Classification Symbols	
Int.Cl.5	C 07 C 235/00 C 07 D 211/00	C 07 C 203/00 C 07 D 213/00
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched*		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <sup>9</sup>		
Category <sup>c</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	EP,A,0366004 (BOEHRINGER MANNHEIM) 2 May 1990, see examples; claims ---	1-7
A	US,A,3096336 (FERGUSON) 2 July 1963, see the whole document ---	1-7
A	EP,A,0083256 (KOWA CO. LTD) 6 July 1983, see page 9, lines 12-24; examples; claims (cited in the application) ---	1-7
A	EP,A,0300400 (FUJISAWA PHARMACEUTICAL CO.) 25 January 1989, see examples; claims (cited in the application) ---	1-7
A	US,A,4200640 (NAGANO et al.) 29 April 1980, see the whole document (cited in the application) --- -/-	1-7
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
30-09-1991	28.10.91	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	 Mme. M. van der Drift	

## III. DOCUMENTS CONSIDERED TO BE RELEVANT

(CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	Chemical Abstracts, vol. 103, 8 July 1985, (Columbus, Ohio, US), J. Xu et al.: "A new vasoactive agent - acesaniamide", see page 34, abstract 349r, & Yiyao Gongye 1985, 16(2), 65-6 -----	1-7

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9101326

SA 49152

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 22/10/91. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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		AU-A-	4354489	26-04-90
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		JP-A-	2169570	29-06-90
		US-A-	5030641	09-07-91
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US-A- 3096336		None		
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		JP-B-	61008057	11-03-86
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		AT-B-	360536	12-01-81
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		AU-A-	2353277	28-09-78
		BE-A-	853144	01-08-77
		CA-A-	1088944	04-11-80
		CH-A-	633535	15-12-82
		DE-A, B, C	2714713	20-10-77
		FR-A, B	2346334	28-10-77
		GB-A-	1562962	19-03-80
		NL-A-	7703624	04-10-77
		SE-B-	436029	05-11-84

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SA 49152

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4200640		SE-A- 7703868	03-10-77